Protocol Title: A Randomized, Controlled, Phase II Study of the Activity and Safety of Autologous Gene-Modified Cytotoxic T Lymphocytes in HIV-Infected Patients

Scientific Abstract:

The cell-mediated immune response plays an essential role in the host's defense against viral infection. Studies of cytomegalovirus (CMV) and influenza virus for which small animal models are available have revealed that $CD8^+$ cytotoxic T lymphocytes (CTLs) represent the major component of this cellular immunity. Although optimal animal models for HIV infection await development, evidence that $CD8^+$ CTLs represent the major and earliest immune response to HIV infection is supported by correlative data from HIV-infected patients. The clinical data available suggest that a breakdown of the host cell-mediated immune response may be responsible for progression to symptomatic AIDS. *In vitro* studies have not only confirmed that HIV-specific $CD8^+$ T cells exhibit cytolytic activity toward HIV-infected targets, but have also revealed that $CD8^+$ T cells have the ability to inhibit replication of HIV in lymphocyte cultures. Data supportive of the central role of $CD8^+$ T cells in HIV infection suggest that adoptive transfer of HIV-specific $CD8^+$ T cells may have potential as an immunotherapy for HIV-infected individuals.

Cell Genesys, Inc. has designed HLA-unrestricted chimeric T cell receptors that can redirect the antigenic specificity of peripheral blood mononuclear cell (PBMC)-derived $CD8^+$ T cell populations to recognize HIV antigen(s) of choice expressed on the surface of infected cells. Upon binding to viral antigen, these receptors initiate T cell activation, resulting in induction of effector functions including cytolysis of the viral-infected cell. We have developed chimeric receptors composed of antigen recognition and signaling domains. The receptor chosen for clinical investigation is composed of the extracellular domain of the human CD4 receptor fused to the cytoplasmic domain of the zeta chain of the T cell receptor. CD4 recognizes the gp120 moiety of the HIV envelope, and zeta is responsible for signal transduction in T cells. Using retroviral-mediated transduction with replication-defective retroviral vectors, we can routinely generate $CD8^+$ T cells expressing high, stable levels of CD4-zeta. The CD4-zeta $CD8^+$ T cell population exhibits highly efficient cytolytic activity against T cells infected with HIV-l laboratory strains and patient isolates.

In the proposed clinical study, we will assess the activity and safety of adoptive transfer of autologous CD4-zeta $CD8^+$ T cells in patients with HIV infection. The proposed study is a randomized, controlled, open-label, two-arm, two center study comparing treatment effect with antiretroviral agents alone to antiretroviral agents plus multiple doses of 10^9 CD4-zeta $CD8^+$ T cells. Antiviral activity, safety, and longevity of the CD4-zeta $CD8^+$ T cells *in vivo* will be monitored.